

25-Hydroxycholesterol Protects Host against Zika Virus Infection and Its Associated Microcephaly in a Mouse Model.

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Authors: Chunfeng Li, Yong-Qiang Deng, Shuo Wang, Feng Ma, Roghiyh Aliyari, Xing-Yao Huang, Na-Na Zhang, Momoko Watanabe, Hao-Long Dong, Ping Liu, Xiao-Feng Li, Qing Ye, Min Tian, Shuai Hong, Junwan Fan, Hui Zhao, Lili Li, Neda Vishlaghi, Jessie E Buth, Connie Au, Ying Liu, Ning Lu, Peishuang Du, F Xiao-Feng Qin, Bo Zhang, Danyang Gong, Xinghong Dai, Ren Sun, Bennett G Novitch, Zhiheng Xu, Cheng-Feng Qin, Genhong Cheng

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Public Summary:

Zika virus (ZIKV) has become a public health threat due to its global transmission and link to severe congenital disorders. The host immune responses to ZIKV infection have not been fully elucidated, and effective therapeutics are not currently available. Here, we identified a molecule called 25-hydroxycholesterol (25HC) that is produced by cells in response to ZIKV infection. While the endogenous production of 25HC does not suffice to ward off ZIKV, we found that augmentation with synthetically derived 25HC can provide significant protective benefits, blocking viral entry in cultured cells, and infection of both mice and rhesus macaques exposed to ZIKV. Moreover, we found that 25HC administration can markedly reduce ZIKV-associated neural tissue damage in human cortical organoids/mini-brains and in developing micel. Collectively, our findings highlight the protective role of 25HC as a natural antiviral agent to combat ZIKV infection and prevent ZIKV-associated outcomes, such as fetal brain damage.

Scientific Abstract:

Zika virus (ZIKV) has become a public health threat due to its global transmission and link to severe congenital disorders. The host immune responses to ZIKV infection have not been fully elucidated, and effective therapeutics are not currently available. Herein, we demonstrated that cholesterol-25-hydroxylase (CH25H) was induced in response to ZIKV infection and that its enzymatic product, 25-hydroxycholesterol (25HC), was a critical mediator of host protection against ZIKV. Synthetic 25HC addition inhibited ZIKV infection in vitro by blocking viral entry, and treatment with 25HC reduced viremia and conferred protection against ZIKV in mice and rhesus macaques. 25HC suppressed ZIKV infection and reduced tissue damage in human cortical organoids and the embryonic brain of the ZIKV-induced mouse microcephaly model. Our findings highlight the protective role of CH25H during ZIKV infection and the potential use of 25HC as a natural antiviral agent to combat ZIKV infection and prevent ZIKV-associated outcomes, such as microcephaly.

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